# Synthetic Approaches to the Alkaloids of the Ancistrocladacea: Dehydroancistrocladisine

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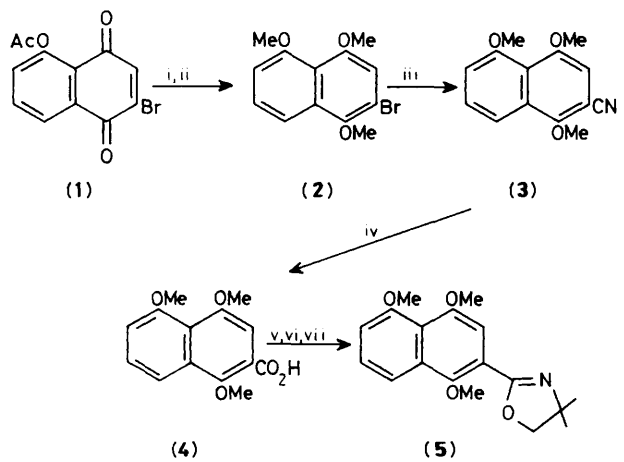
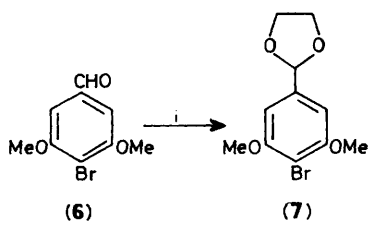
Dehydroancistrocladisine, a derivative of ancistrocladisine which is a member of the unusual naphthyl-isoquinoline group of alkaloids, has been synthesized by a route which can be adapted to provide asymmetric syntheses of these alkaloids.

The naphthyl-isoquinoline alkaloids of the plant family Ancistrocladacea are of unusual biogenesis and exhibit the distinctive features of a methyl group at the 3-position and of oxygenation at the 6- and 8-positions of the isoquinoline ring. Many of these alkaloids occur as thermally stable atropisomers.[1] Little synthetic work has been carried out in this area[2] and we now report the synthesis of racemic dehydroancistrocladisine (**16**) (Scheme 3), a derivative of the alkaloid ancistrocladisine (**15**),[3] by a method which can be adapted to provide an asymmetric synthesis of the *Ancistrocladus* alkaloids.

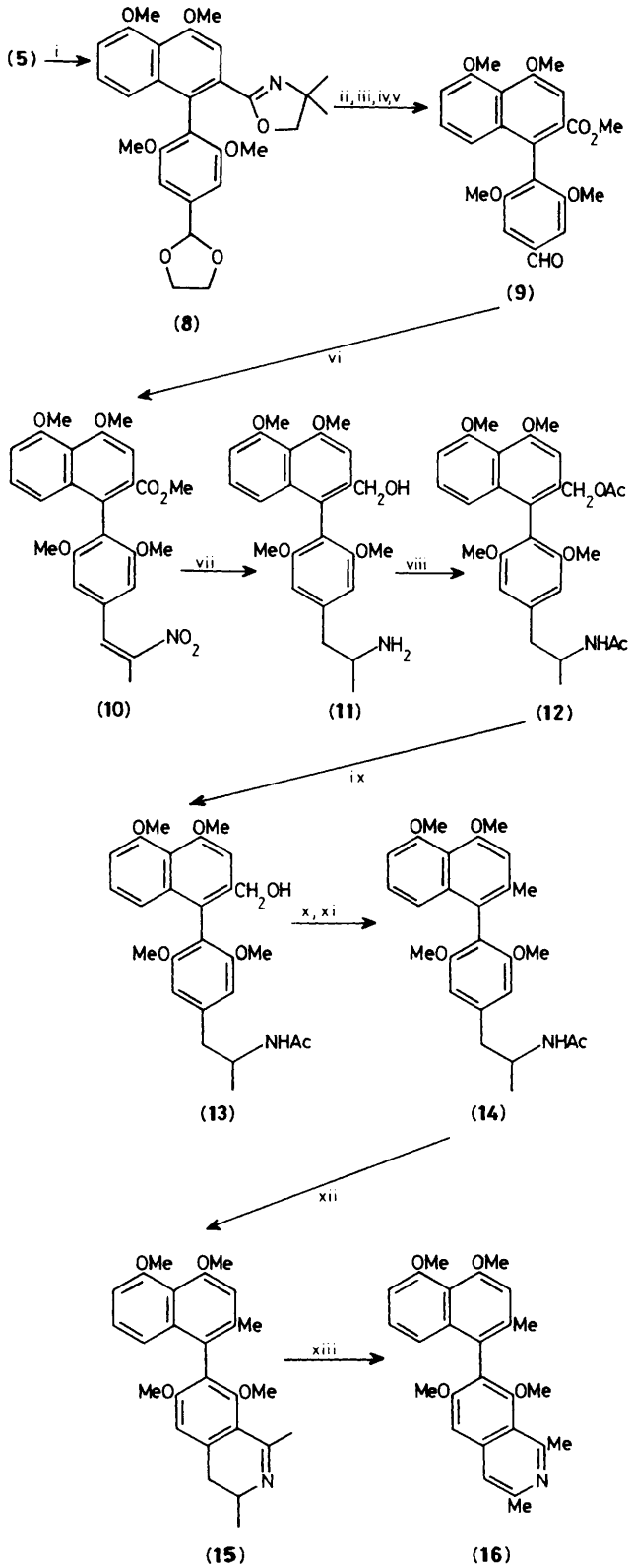
We planned to construct the biaryl linkage of dehydroancistrocladisine (**16**) by using the biaryl synthesis of Meyers in which the *ortho*-methoxy group in an *o*-(methoxyaryl)oxazo-




**Scheme 1.** *Reagents and conditions*: i, $Na_2S_2O_4$; ii, $Me_2SO_4$, aq. NaOH, $Bu_4NBr$, ether; iii, CuCN, dimethylformamide (DMF), reflux 16 h; iv, KOH, MeOH, $H_2O$, reflux 72 h; v, $(COCl)_2$, $CH_2Cl_2$, 25 °C, 2.5 h; vi, $HOCH_2CMe_2NH_2$, $CH_2Cl_2$, 25 °C, 2 h; vii, $SOCl_2$, $CH_2Cl_2$, 1.5 h, 25 °C.




**Scheme 2.** *Reagents and conditions*: i, $HOCH_2CH_2OH$, PhH, *p*-$MeC_6H_4SO_3H$, reflux 20 h.




**Scheme 3.** *Reagents and conditions*: i, 3 equiv. Grignard reagent of (**7**), tetrahydrofuran (THF), 25 °C, 16 h, reflux 2 h; ii, $MeNO_2$, MeI, 70 °C, 24 h; iii, NaOH, $H_2O$, MeOH, THF, reflux 35 h; iv, $H^+$; v, MeI, DMF, $K_2CO_3$, 25 °C, 16 h; vi, $EtNO_2$, $NH_4OAc$, AcOH, 80 °C, 1.5 h; vii, $LiAlH_4$, THF, reflux 2.5 h; viii, $Ac_2O$, $C_5H_5N$, 35—40 °C, 2.5 h; ix, NaOMe, MeOH, 25 °C, 1.5 h; x, $Me_3SiCl$, NaI, MeCN, 35—40 °C, 1 h; xi, Zn, AcOH, 80 °C, 4.5 h; xii, $POCl_3$, MeCN, reflux 0.5 h; xiii, W2 Raney nickel, $C_{10}H_8$, reflux 3 h.

line is displaced by an aryl Grignard reagent.[4] For this purpose we required the oxazoline (**5**) (Scheme 1) and the bromo-compound (**7**) (Scheme 2).

For the synthesis of the oxazoline (**5**) the known bromojuglone (**1**) was smoothly converted, in an adaptation of the method of Jung and Hagenah,[5] into the bromonaphthalene (**2**) (73%), m.p. 115—116 °C. This was caused to react with copper(I) cyanide and the resultant nitrile (**3**)† (94%), m.p. 125.5—126 °C, on hydrolysis afforded the acid (**4**)† (100%), m.p. 124—125 °C. Conventional steps then allowed the conversion of the acid (**4**) into the required oxazoline (**5**)† (85%), m.p. 101—102 °C. The bromo-compound (**7**)† (98%), m.p. 45—47 °C was readily available by ketalization of the known aldehyde (**6**).[6]

An excess of the Grignard reagent derived from the bromo-compound (**7**) (Scheme 3) was allowed to react with the oxazoline (**5**) and the resultant biaryl (**8**)† (81%), m.p. 160—161 °C was converted by deprotection and methylation into the intermediate (**9**)† (90%), m.p. 246—247 °C. Henry reaction then gave the nitrostyrene (**10**)† (80%), m.p. 199—200 °C. On reduction this latter compound supplied the racemic amphetamine (**11**)† (82%), m.p. 104—106 °C, which on acetylation afforded the *N*,*O*-diacetyl compound (**12**)† (87%), m.p. 178—179.5 °C. *O*-Deacetylation of this last-mentioned compound was achieved with sodium methoxide in methanol and the resultant alcohol (**13**)† (81%), m.p. 161—162 °C, was deoxygenated by the method of Morita *et al.*[7] This afforded the *N*-acetylamphetamine (**14**)† (97%), m.p. 174—175.5 °C which on Bischler–Napieralski cyclization supplied ancistrocladisine (**15**) (94%) as a mixture of diastereoisomers. Dehydrogenation of this mixture afforded racemic dehydroancistrocladisine (**16**)† (23%), m.p. 207—208 °C (lit.,[3] 210—211 °C) which had spectroscopic properties identical with those recorded in the literature.[3]

By use of a chiral oxazoline in the biaryl synthesis[8] it is expected that the presently described methodology will lead to efficient asymmetric syntheses of the *Ancistrocladus* alkaloids. Such experiments are being pursued.

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† New compounds gave satisfactory elemental analyses and spectra in accord with the assigned structures.